II. Rejection Under § 112, First Paragraph

The examiner has maintained the rejection of claim 19, and newly rejected claim 65, under § 112, first paragraph on the grounds that the specification does not provide any evidence that administration of UTAA will "enhance" the production of antibodies. In the previous response, applicants respectfully traversed the rejection, pointing out that claims 19 and 65 were supported by the specification in both diagnostic and therapeutic contexts and, further, offered that the examiner had failed to advance any scientific reasoning against the operability of these claims with respect to either of these endeavors.

In fact, the specification contains more than enough disclosure regarding enhancement of antibody production to support claims 19 and 65. As described in the Background, many melanoma patients have antibodies against UTAA. Page 7, lines 25-33. In such patients, further administration of purified UTAA would be expected to stimulate the production of antibodies, and the examiner has offered no reason why this would not be the case. Finally, in a declaration from one of the inventors, Dr. Rishab Gupta, the antibody titers of four melanoma patients are shown following administration of UTAA in the form of a mixed cell vaccine. In each case, the anti-UTAA titers rose significantly following administration.

The examiner has refuted the declaratory showing on the grounds that the data were generated using whole cells and not purified antigen. While true, the relevance of this distinction is unclear; in effect, why would those of skill in the art believe that the ability to enhance antibody

production to UTAA using a cell membrane-bound form of the antigen would not also indicate that free UTAA could enhance antibody production? Applicants submit that there is no reason to question the ability of free UTAA to act as the cell membrane-bound form does. In fact, it has been shown that free UTAA is a potent antigen in the baboon system. Hunt *et al.*, *Cancer Immunol. Immunother.* 34:377-382 (1992).

For all of these reasons, applicants again submit that the rejection is improper and request reconsideration thereof.

III. Rejection Under 35 U.S.C. § 112, Second Paragraph

The examiner has rejected claims 19 and 65 as indefinite in that they allegedly are duplicates of each other, the former reciting inducing or enhancing antibody production and the latter reciting only enhancing. The examiner argues that because both recite a single step of administering an antigen composition of claim 62, the two claims cannot be substantially different. This is legally incorrect. Would the examiner argue that a single step of administering the antigen composition is the same in an mouse and a human? Are intravenous and intramuscular routes of administration also the same? These claims surely would be accepted as proper dependent claims in the same application. Moreover, claim 65 clearly has a different scope than claim 19, as claim 19 contemplates either induction or enhancement of antibodies. Thus, these claims are not "duplicates" as alleged by the examiner. Applicants have amended claim 65 in order to make this point more apparent.

In light of the foregoing comments and the offered amendment, reconsideration and withdrawal of the rejection is respectfully requested.

IV. Rejection over Real

Claims 19 and 62 are rejected under § 102(b) as allegedly anticipated by Real *et al.* (U.S. Patent 4,562,160; "Real"). Real is said to disclose an antigen composition comprised of a tumor associated antigen having a molecular weight of 90-100 kD which is useful for antibody production. The examiner argues that UTAA may be Real's antigen, designated "FD."

Applicants have provided a variety of reasons why the Real antigen cannot be UTAA. First, applicants have noted that there appears to be a considerable size difference between UTAA and FD under non-reducing conditions. Second, the tissue distribution of FD is much smaller than UTAA in melanoma patients. And third, applicants have provided a table listing further distinguishing characteristics of UTAA and FD.

The examiner's only response to these submissions is to argue that the table contains properties that are not "claim limitations" and, hence, applicants are not entitled to rely on those distinctions. This is incorrect as a matter of law. The rejected claims recite UTAA, and UTAA has the properties listed in the table of the last response. There is no basis for arguing that each and every characteristic of UTAA needs to be recited in the claims. Rather, the specification defines UTAA both physically and immunologically; the properties of the antigen thus defined are relevant to its identity regardless of whether they are actually recited in the claim.

In light of the foregoing comments, applicants respectfully submit that the FD antigen of Real cannot be the same as UTAA and, hence, the rejection is improper. Reconsideration and withdrawal is respectfully requested.

V. Rejection Over Euhus

Claims 19 and 62-64 are again rejected as anticipated or rendered obvious by Euhus *et al.* ("Euhus"). According to the examiner, Euhus discloses a 110 kD version of UTAA that appears to be the same antigen as that claimed, or at least an obvious variation thereof. In addition, Euhus is said to disclose the production of antibodies, implying the administration of the antigen to an animal for the purpose of eliciting UTAA-reactive antibodies. Applicants respectfully traverse the rejection.

Applicants again note that the Euhus abstract is not enabling for the production of UTAA. It is well established that a reference must teach how to make and use, *i.e.*, must enable the claimed invention for it to be a valid reference against the claims of an application. In *Paperless Accounting Inc. v. Bay Area Rapid Transit Sys.*, 231 U.S.P.Q. 649 (Fed. Cir. 1986), the PTO's reviewing court said that a "§ 102(b) reference 'must sufficiently describe the claimed invention to have placed the public in possession of it'.... '[E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling.'"

Turning to the abstract, it is true that an antibody specific for UTAA is disclosed. In addition, fractionation methods for isolating antibodies from human sera and the association of UTAA with IgM and IgG fractions of antigen-positive sera are taught. None of the foregoing is relevant, however, to the question of anticipation (or obviousness) of an invention relating to an antigen composition or methods of immunization. In order for these claims to be enabled, at a minimum, one must have an antibody that binds to the antigen of question - UTAA. Thus, the disclosure must provide the antibody itself (which is impossible unless it is specifically described and deposited), or the disclosure must provide information sufficient to allow the reliable and repeatable generation of an antibody comparable to the disclosed antibody. In this case, that would involve providing a UTAA antigen (*i.e.*, the protein sequence) or methods permitting the reliable and repeatable purification of UTAA. In other words, merely disclosing "an antibody for UTAA" does not provide an enabling disclosure therefor, and thus does not place the antibody or the antigen in the hands of the public.

The abstract states that "U-TAA was recovered from some sera free of IgG and IgM by anion exchange chromatography." It might be argued this disclosure is sufficient to place UTAA in the hands of the public; this simply is not the case. In the accompanying declaration of Dr. Ralph Reisfeld, Head of the Department of Molecular Immunology at the Scripps Institute, Dr. Reisfeld states that the Euhus abstract would not be enabling for UTAA or for methods relating to the diagnosis of melanoma using UTAA or UTAA-specific antibodies. In particular, "key conditions such as the proper pH or ionic strength under which isolation was conducted are missing, as are the migration distances or retention times for gel or column

purification." According to Dr. Reisfeld, the absence of these details prevents the reproducible isolation and purification of UTAA.

Thus, it again is respectfully submitted that the Euhus abstract is not enabling for the claimed compositions or methods. The disclosed antibody was not available to the public nor could a comparable one have been reproduced given the lack of any meaningful disclosure regarding the identity of UTAA or how one could isolate UTAA. Reconsideration and withdrawal of the rejection is respectfully requested.

VI. Rejection Over Paulie

Claims 62-64 are again rejected as anticipated or rendered obvious by Paulie *et al.* ("Paulie"). According to the examiner, Paulie discloses a 92 kD antigen associated with bladder carcinoma that appears to be same antigen as that claimed, or at least an obvious variation thereof. Applicants respectfully traverse the rejection.

In their last response, applicants provided a declaration from one of the inventors, Dr. Rishab Gupta. The declaration showed that the antigen identified by Dr. Paulie is immunologically unrelated to 90-100 kD subunit of UTAA. The examiner has dismissed that data in light of the following concerns:

(1) The examiner questions the identity and source of the antibody P7A5.
(2) The examiner questions the antigen preparation.
(3) The examiner questions the source and character of the C6 antibody.
(4) The examiner questions the lack of molecular weight markers.

First, with respect to antibody P7A5, applicants attach a letter from Dr. Staffan Paulie. Therein, it is explained that antibody P7A5 is directed to the same antigen as that described in the Paulie reference. Second, the antigen preparation protocol by which both batches of UTAA were generated is as described in the specification. Third, the C6 antibody is, in fact, the same as antibody AD1-40F4 of the present application. C6 is simply the nickname by which this antibody has been referred to in the inventors' laboratories. And fourth, it is not understood why the examiner objects to the lack of molecular weight standards in FIG. 1 of the declaration. Comparison of reactive species identified with C6 in Western blots provides an adequate comparison of UTAA with the 92 kD Paulie antigen, regardless of their molecular weight. Nonetheless, applicants point out that the molecular weight standards for FIG. 2 and FIG. 3 of the declaration are 106, 80, 49.5, 32.5, 27.5 and 18.5 kD, from tope to bottom in the lane marked "STD MW". All of these comments are supported by the attached declaration of Dr. Gupta. Therefore, it is again submitted that UTAA and the 92 kD antigen of Paulie are distinct.

Turning to the obviousness rejection, there is nothing in the Paulie reference to suggest the antigen designated as UTAA, which has now been shown as distinct from Paulie's 92 kD antigen. Again, any comparison of the Paulie antigen with UTAA is pure hindsight and cannot be supported. Applicants therefore respectfully request reconsideration and withdrawal of both rejections.

VII. Summary

In light of the foregoing amendments and remarks, applicants submit that all claims are in condition for allowance and solicit an early indication to that effect. Should Examiner Sidberry feel that further discussion of any remaining issues would advance the prosecution, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

STEVEN L. HULTQUANDER
REG. NO. 37,642
FOR David L. Parker
Reg. No. 32,165
Attorney for Applicants

April 26, 1996

ARNOLD, WHITE & DURKEE
P. O. Box 4433
Houston, TX 77210
(512) 418-3000